Ketone Monitoring Device

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***Abstract* — Diabetic ketoacidosis (DKA) is a complication of diabetes that results from high levels of ketones in the bloodstream. If left untreated, mortal outcomes in a patient will likely occur within a couple of weeks. DKA has commonly been diagnosed through urine ketone testing, however this form of testing has its limitations. In this paper, we explore an alternative blood test to determine ketone levels based on the reaction catalyzed by the enzyme β-hydroxybutyrate dehydrogenase. We utilize gold electrodes to measure the presence of ketones in the blood stream. This signal is then run through a circuit consisting of a transimpedance amplifier, inverting amplifier, low pass filter, comparators, and logic gates that determines if the patient has normal, at risk, or DKA ketone levels through a series of LED lights. Additionally, the circuit outputs a voltage that is sent to a microcontroller and shown on an alphanumeric display for a more precise reading of the ketone level. It is important to ensure this device is calibrated to the relative ketone levels of the patient so that accuracy and relative conversions are maintained in its calculations.**

Keywords — diabetic ketoacidosis, ketones, blood test, electrodes

I. Introduction

Diabetes is a chronic health condition where either the pancreas does not create enough insulin (type I) or the body cannot use it effectively (type II). Insulin is a hormone made in the pancreas that plays a key role in regulating the body's metabolism of carbohydrates, fats, and proteins. It lets sugar molecules in the bloodstream that have been broken down from consumed food into the body's cells to be used for energy [1]. When there is not enough insulin or the body stops responding to it, blood sugar builds up in the bloodstream and can lead to health problems such as heart and kidney disease. Without insulin, the body begins to break down fat for fuel which produces acids called ketones. A buildup ketones in the bloodstream combined with high blood glucose levels can lead to diabetic ketoacidosis (DKA), which can be life-threatening. DKA is most common in patients with type-I diabetes. It is characterized by hyperglycemia, acidosis, and ketonemia [2]. Normal ketone blood levels are typically less than 0.6 mmol/L. Slightly high ketone blood levels are between 0.6 and 1.5 mmol/L. Ketone blood levels between 1.5 and 3 mmol/L indicate DKA risk and above 3 mmol/L indicates DKA.

There are many factors that may lead to DKA including non-compliance, new-onset diabetes, and infections such as pneumonia and urinary tract infections [2]. Although the prevalence of DKA varies annually, it is estimated to affect around 5-8% of adults with type-I diabetes and has a mortality rate of 0.38% [3].

The common method of diagnosis for DKA has been through urine ketone testing. A urine reagent strip relies on a nitroprusside reaction which causes a color change as the indicator of the presence of ketones. A limitation to this is that since the ketone sample is produced from testing urine externally, the results do not represent the current levels in the patient at that moment, there is some delay. This means a positive reading can be produced even after the DKA has been resolved. Additionally, the test only indicates if small, moderate, or large amounts of ketones are present, creating user variability in interpreting color changes [4]. Continuous or frequent monitoring of ketone levels for patients at risk of DKA is also difficult as forcing them to urinate repeatedly for tests is not ideal.

In addition to this, a benefit of having a fast and blood-based test of ketones gives insight into the metabolic health of diabetes patients, allowing for maintenance of nutritional ketosis, a metabolic state that allows for better use of ketones as fuel and stabilization of blood sugar and insulin release, leading to weight loss, decreasing hunger, and increasing satiety [5]. Nutritional ketosis in diabetic patients promotes a metabolic shift towards lipid oxidation, utilization of fatty acids, and the efficient use of ketones as energy- all of which lead to a healthier lifestyle, as metabolic flexibility granted by nutritional ketosis is something that allows humans to use ketones to supply nearly every type of cell in the body [5].

II. Chemistry

β-hydroxybutyrate (BHB) is a ketone body synthesized in the liver from fatty acids. It is a carrier of energy from the liver to the peripheral tissues when the supply of glucose is too low for the body's energetic needs. When the body is not able to metabolize enough energy from glucose, it uses adipose tissues as its main energy source to prevent cellular starvation and death. Free fatty acids move to the mitochondria and undergo beta oxidation which converts them to acetyl coenzyme A (acetyl-CoA). To be used as energy by cells, acetyl-CoA bonds with acetoacetic acid (AcAa) which is also converted to BHB and acetone, both of which are ketone bodies. Under normal conditions the ratio of AcAa and BHB is relatively stable at 1:1 but increased free fatty acid oxidation favors the production of BHB, skewing the ratio during DKA [3].

When BHB in the blood comes into contact with NAD^+ in the presence of the enzyme, β-hydroxybutyrate dehydrogenase, an oxidation reaction, shown in (1) is initiated.

$$C_4H_8O_3 + NAD^+ \rightleftharpoons C_4H_6O_3 + NADH \quad (1)$$

BHB is oxidized to acetoacetate (AcAc) and NAD^+ is reduced to NADH, as seen in Fig. 1. The amount of NADH produced is proportional to the concentration of BHB in the sample.

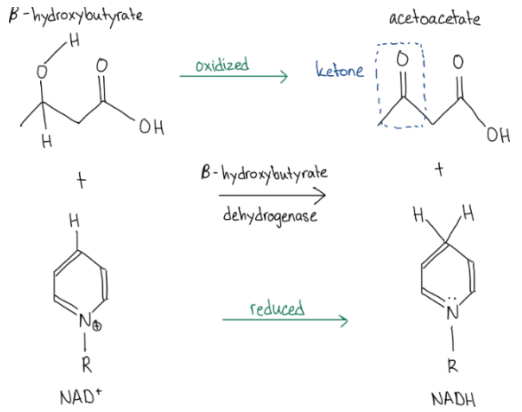

Figure 1: Oxidation reaction caused by β-hydroxybutyrate dehydrogenase

III. Methods

The design of our ketone measurement device is broken down into a biosensor and a signal processing circuit.

A. Biosensor design

Our ketone biosensor consists of a 3-electrode design. The test strip contains a working electrode, reference electrode, and counter electrode (Fig. 2). The reaction between BHB and AcAc occurs at the working electrode, so the corresponding oxidation of NADH is monitored at the electrode surface. A gold electrode was chosen for the working electrode because the gold material best facilitates the electron transfer from NADH as it oxidizes back to NAD^+ . The electron from this oxidation process is used to generate a current that is proportional to the concentration levels of BHB from the blood sample. At the reference electrode, the potential generated is used as a reference to control and measure the potential generated by the working electrode. Finally, the counter electrode is used to balance the reaction at the working electrode.

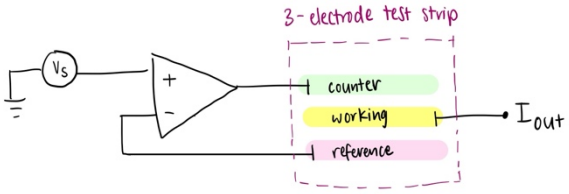

Figure 2: 3-electrode test strip design, with the counter, working, and reference electrode configurations.

B. Current estimation and design calibration

The output current of the working electrode serves as an input for the ketone-monitoring circuit, where the current is proportional to the concentration of BHB in the blood sample. An estimate for the magnitude of output current was derived from existing research on ketone sensors using the reaction between BHB and AcAc [4]. The graph in Fig. 3 shows the experimental results for current values corresponding to AcAc levels for diabetic ketoacidosis.

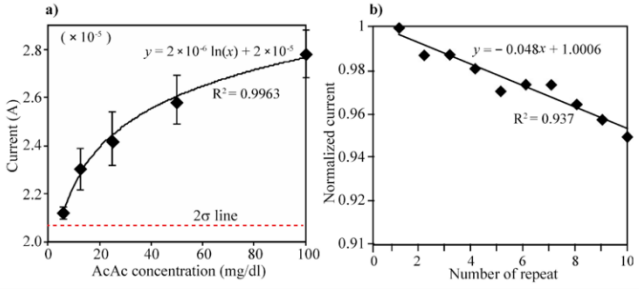

Figure 3: Experimentally-determined values for DKA concentration of ketone relative to produced current [4].

For an estimate of the current corresponding to the minimum threshold for DKA, the current corresponding to 3.0 mmol/L of BHB was used. This concentration was converted to mg/dL of AcAc in the following manner:

$$\frac{3\ mmol\ BHB}{L} = \frac{3\ mmol\ AcAc}{L} = \frac{0.0003\ mol\ AcAc}{dL}$$

$$\frac{0.0003\ mol\ AcAc}{dL} \cdot \frac{101.08\ g\ AcAc}{mol} = \frac{0.0303\ g\ AcAc}{dL} = \frac{\mathbf{30.03\ mg\ AcAc}}{\mathbf{dL}}$$

From the graph, the current corresponding to this AcAc concentration was estimated as 25µA, representing the minimum threshold for DKA. However, due to a limited amount of research on the current correspondence of ketone and the dependence of current on the volume of blood sampled, the exact magnitude for the input of our circuit remains unknown. Because of this, a calibration step must be performed before use of the device. The sensor should be calibrated to determine the current value from a blood sample with a known concentration of ketone.

For the purpose of analyzing the signal processing circuit of the device (as shown in section *C.*), an arbitrary DKA input current of 26µA was selected, and values of circuit components were determined based on this. For actual use of the device, the values of the circuit components may be adjusted based on the calibration step.

C. Signal processing circuit

The biosensor transduces the beta-hydroxybutyrate concentration levels into a current at the working electrode. This current is then used as the input for the ketone-monitoring circuit, composed of 5 elements: transimpedance amplifier, inverting amplifier, low pass filter, comparators, and logic gates (Fig. 4).

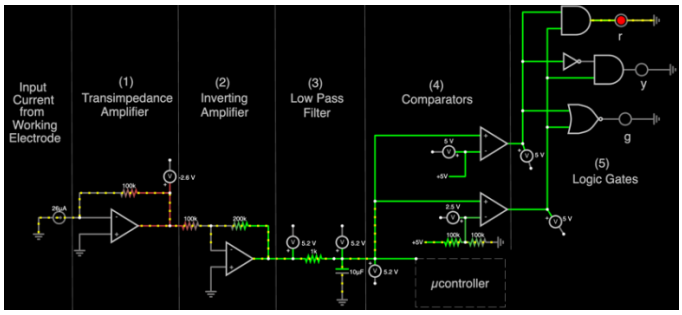

Figure 4: Full circuit schematic, starting with the current input from the working electrode, ending with the LED indicators and microcontroller display.

The first three components serve to convert the current from the working electrode into a voltage, then amplify and filter the signal voltage. The signal amplification and filtering components are shown below (Fig. 5).

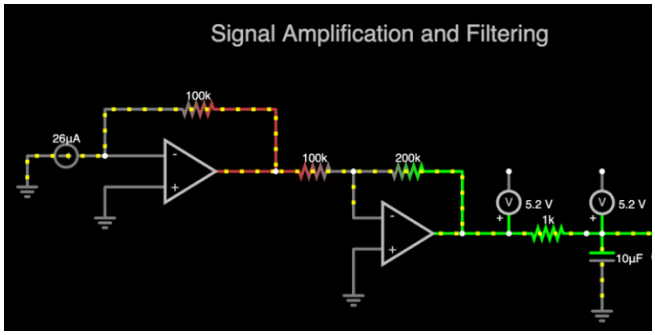

Figure 5: The first three components of the circuit, consisting of a transimpedance amplifier, inverting amplifier, and low pass filter. These components serve to amplify and filter the signal.

The input current is first processed in a transimpedance amplifier, which outputs a negative voltage in (2).

$$V = -I_{in}R \quad (2)$$

The negative voltage outputted by the transimpedance amplifier goes into an inverting amplifier. This element outputs an amplified, positive voltage (3) using a gain of -2 dB (4).

$$V_{out} = -(R_f / R_i)\, V_{in} \quad (3)$$

$$G = -(R_f / R_i) = -(200k\Omega / 100k\Omega) = -2 \quad (4)$$

To decrease excess noise signals, a low pass filter blocks higher frequency signals. The response of the first-order low pass filter is described by an s-domain transfer function, where the variable s represents complex frequency (5). The cutoff frequency, or the frequency at which the filter's amplitude response is reduced by 3 dB, is about 16 Hz (6).

$$H(s) = RC / (s + RC) \quad (5)$$

$$f_c = w_c / 2\pi = 1 / 2\pi RC = 15.92\ Hz \quad (6)$$

The output voltage of these components goes into the next part of the circuit, which is responsible for indicating the diagnostic status of DKA. These components are shown below in Fig. 6.

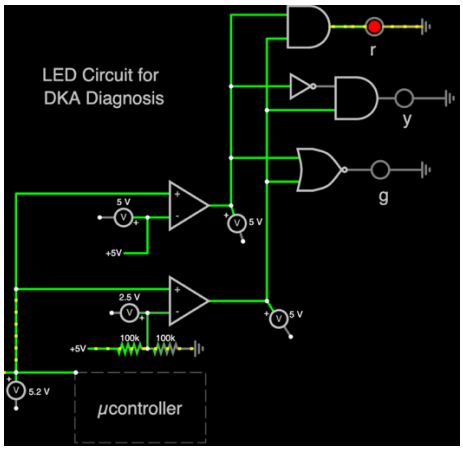

Figure 6: Comparator and logic gates to light up the current LED light corresponding to ketone concentrations.

The output voltage from the low pass filter is fed into two comparators, each of which compare the signal voltage to a reference voltage. The comparators are used as an indicator of the presence and risk of diabetic ketoacidosis. The top comparator has a reference voltage which corresponds to the minimum signal voltage with presence of DKA. The comparator outputs the positive rail (+5 V) if the signal voltage is higher than the reference voltage, or the negative rail (-5 V) if the signal voltage is less than the reference. The second comparator has a reference voltage which corresponds to the minimum signal voltage with risk of DKA. Similarly, the comparator outputs +5 V when the signal is greater than the reference, or -5 V when the signal is less than the reference. The reference values used for the top and bottom comparators are 5 V and 2.5 V, respectively. The source voltage would come from a 5 V battery. However, these values would need to be adjusted after the calibration step to account for the specific cutoffs for each range of ketone concentration.

The signals from the comparators are interpreted using logic gates, with the binary outputs shown in Fig 7. The red LED light uses an *and* gate. This gate will only signal the LED to light up when it receives two binary 1 inputs from the comparators. This will happen when the comparators both receive a signal that exceeds 5 V, causing the output of both comparators to be V+. This voltage represents a DKA ketone concentration (greater than 3.0 mmol/L). Next, the yellow LED lights up when the comparators receive an input voltage between 2.5 and 5 V. This means the first comparator outputs V- and the second comparator outputs V+. An inverter converts the V- output from the first comparator into a binary 1, so the *and* gate used by the yellow LED receives two binary 1 inputs. This voltage represents an "at risk" ketone concentration (between 1.5 mmol/L and 3.0 mmol/L). Finally, the green LED lights up when the signal voltage is less than 2.5 V. Both comparators output a binary 0, so the green LED uses a *nor* gate to output a binary 1 causing the green LED to light up. This voltage represents a normal ketone concentration (less than 1.5 mmol/L).

Red LED: *and* gate

INPUT A	INPUT B	OUTPUT
0	0	0
1	0	0
0	1	0
1	1	1

Yellow LED: *inverter* + *and* gate

INPUT A	OUTPUT
0	1
1	0

INPUT A	INPUT B	OUTPUT
0	0	0
1	0	0
0	1	0
1	1	1

Green LED: *nor* gate

INPUT A	INPUT B	OUTPUT
0	0	1
1	0	0
0	1	0
1	1	0

Figure 7: Logic gate charts showing when the red, yellow, and green LEDs will light up. The red LED only lights up when both inputs are high. The yellow LED only lights up when the first input is low and the second is high. The green LED only lights up when both inputs are low.

In addition to the LED indicator of ketone levels, the circuit also sends voltage to a microcontroller. The microcontroller processes the voltage and outputs to an alphanumeric display to provide a reading of the exact ketone concentration level.

D. Falstad simulation results

The full circuit was simulated on the Falstad Java applet using current inputs of 26 µA, 15 µA, and 10 µA, respectively representing DKA ketone concentration, at-risk ketone concentration, and normal ketone concentration. The simulation results are shown below in Fig. 8 and 9.

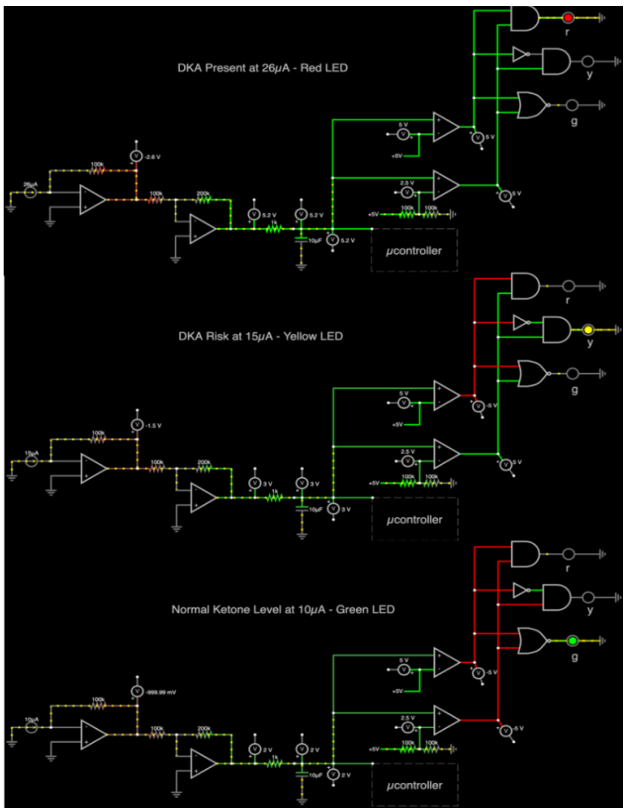

Figure 8: Circuit diagram on Falstad with an input current of 26µA, corresponding to a ketone concentration level slightly above 3.0 mmol/L, indicating presence of diabetic ketoacidosis lighting the red LED. Under, an input current of 15µA, corresponding to a ketone concentration level estimated between 1.5 mmol/L and 3.0 mmol/L, indicating risk of diabetic ketoacidosis triggering the yellow LED. Lastly, an input current of 10µA, corresponding to a ketone concentration level less than 1.5 mmol/L, indicating normal blood ketone levels and lighting a green LED.

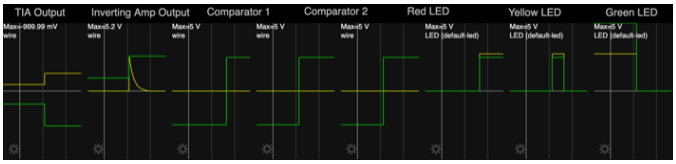

Figure 9: Simulation of circuit components showing range of current and output voltages as input changed from 10μA to 26μA, referencing normal ketone levels triggering the green LED, to presence of DKA triggering the red LED.

As shown in Fig. 8 and Fig. 9, each LED lit up for its respective ketone concentration range, indicating that the circuit works as expected to accurately diagnose DKA. In addition to the LED indicators, the microcontroller would also convert the signal voltage back into the ketone concentration and display the exact concentration value for the user (not pictured in Falstad).

IV. Conclusion

Our development and analysis of this novel blood ketone monitoring device allows a promising alternative to traditional urine ketone testing for detection of diabetic ketoacidosis. Utilizing real-time price measurements of β-hydroxybutyrate provided through our circuit, along with subsequent signal processing, allows for accurate assessment of ketone levels for consistent monitoring. Our use of a transimpedance amplifier, unity gain buffer, inverting amplifier, low pass filter, comparators, and logic gates, allow us to efficiently translate these measurements into clear, actionable outputs that will better help those struggling with their ketone levels. The main advantage of our device is its ability to provide immediate and accurate ketone level readings, which is critical for the effective management of DKA, especially in emergency situations. This immediate feedback loop allows for timely medical interventions, potentially reducing the mortality and morbidity associated with DKA.

However, our design still does come with some limitations. The need for the device to be calibrated to individual patient ketone levels to ensure accuracy, as well as the complexity of our circuit, both pose as potential challenges for device development and clinical adoption. Improvements upon these limitations would be focused on simplifying the calibration to be easier and more user-friendly, reducing the need for clinical adjustments to the device or anything that can't be done by the patient at home. Also, extensive clinical testing and data needs to be collected on device performance to ensure efficacy and accurate measurements across different patient populations and different calibrations.

Overall, this device represents a big step forward in terms of ketone monitoring for patients and the management of diabetes and diabetic ketoacidosis. With further fool-proofing, development and validation, it is very possible for this tool to become essential in home-based user-friendly ketone monitoring and health management.

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